PUBLIC SUMMARY DOCUMENT
Product: Sertindole, tablet, 4 mg, 12 mg, 16 mg, 20 mg, Serdolect®
Sponsor: Lundbeck Australia Pty Ltd
Date of PBAC Consideration: March 2011

1. Purpose of Application

The submission sought an Authority required (STREAMLINED) listing for the treatment of schizophrenia in patients who have had prior treatment with at least one other antipsychotic.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Sertindole was TGA registered on 6 July 2010 for the treatment of schizophrenia. Due to cardiovascular safety concerns, sertindole should be used only for people who are not responsive to, or intolerant of at least one other antipsychotic medicine. Due to its slow onset of action, sertindole should not be used in emergency situations for urgent relief of symptoms in acutely disturbed patients.

4. Listing Requested and PBAC's View

Authority required (STREAMLINED)
For treatment of schizophrenia in people who have had prior treatment with at least one other anti-psychotic.

Not be used in emergency situations for urgent relief of symptoms in acutely disturbed people.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Schizophrenia is a severe psychiatric illness, which is likely to affect seven in every thousand Australians during their lifetime. It is characterised by disturbances in speech, perception, cognition, volition and emotion. Males are more commonly and more severely affected than females. Peak age of onset is in the late teens and early twenties. Atypical antipsychotics such as risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole are usually used as first-line treatment as they are associated with fewer side effects, although multiple switches between drugs may be required. Clozapine and typical antipsychotics are generally trialled if treatment with several atypical antipsychotics has failed.

The submission proposed that the place of sertindole is as an alternative second line treatment of schizophrenia.

6. Comparator

The submission nominated risperidone as the main comparator, with olanzapine as a secondary comparator.

The PBAC considered that olanzapine was a more appropriate choice of main comparator than risperidone.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented two head-to-head randomised trials (M95-372, 97203) comparing sertindole with risperidone using post-hoc analyses (re-definition of ITT populations), one head-to-head randomised comparative trial comparing sertindole with olanzapine (11286) and one randomised, open label, long term trial comparing the safety of sertindole with risperidone (99824). Supportive analyses were provided in an indirect meta-analysis of 4 trials comparing sertindole with haloperidol and 8 trials comparing olanzapine with haloperidol, using haloperidol as common comparator. Four Cochrane reviews are also presented as supporting evidence.

The table below details the published trials presented in the submission:

Trial ID/First author	Protocol title/ Publication title	Publication citation
Sertindole vs Risperidone (Direct randomised trials)		
Azorin JM et al 2006	A double-blind, controlled study of sertindole versus risperidone in the treatment of moderate-to-severe schizophrenia.	International Clinical Psychopharmacology. 2006, 21(1):49-56.
Supplementary randomised trials		
Thomas S et al 2010	Safety of sertindole versus risperidone in schizophrenia: principal results of the sertindole cohort prospective study (SCoP).	Acta Psychiatr Scand 2010:1-11.
Sertindole vs Haloperidol		
Indirect randomised trials		
Zimbroff DL et al 1997 Hale AS et al 2000 Hale AS et al 2000	Controlled, dose-response study of sertindole and haloperidol in the treatment of schizophrenia. Sertindole Study Group. Sertindole improves both the positive and negative symptoms of schizophrenia: results of a phase III trial. Sertindole is associated with a low level of extrapyramidal symptoms in schizophrenic patients: results of a phase III trial.	The American Journal of Psychiatry. 1997, 154(6):782-91. Int J Psych Clin Pract. 2000a, 4:55-62. Int J Psych Clin Pract. 2000b, 4:47-54.
Olanzapine vs Haloperidol		
Indirect randomised trials		
Beasley et al 1996	Olanzapine versus placebo and haloperidol: Acute phase results of the North American double-blind olanzapine trial.	Neuropsychopharmacology 1996,14: 111-123.
Beasley et al 1997	Olanzapine versus haloperidol: Acute phase results of the international double-blind olanzapine trial.	European Neuro-psychopharmacology. 1997, 7:125-137.
Bernardo et al 2001	Double-blind olanzapine vs. haloperidol D2 dopamine receptor blockade in schizophrenic patients: A baseline-endpoint IBZM SPECT study,	Psychiatry Research Neuroimaging. 2001, 107: 87-97.
Ishigooka et al 2001	Olanzapine versus haloperidol in the treatment of patients with chronic schizophrenia: Results of the Japan multicenter, double-blind olanzapine trial.	Psychiatry and Clinical Neurosciences. 2001, 55: 403-414.
Kongsakon et al 2006	Asian outpatients with schizophrenia: A double-blind randomized comparison of quality	Journal of the Medical Association of Thailand.

Trial ID/First author	Protocol title/ Publication title	Publication citation
	of life and clinical outcomes for patients treated with olanzapine or haloperidol,	2006, 89: 1157-1170.
Lindenmayer et al 2007	A randomized controlled trial of olanzapine versus haloperidol in the treatment of primary negative symptoms and neurocognitive deficits in schizophrenia.	Journal of Clinical Psychiatry. 2007, 68(3):368-79.
Tollefson et al 1997	Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial.	The American Journal of Psychiatry. 1997, 154:457-465.
Volavka et al 2002	Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder.	American Journal of Psychiatry. 2002, 159:255-262.
Meta-analyses of randomised trials		
Lewis R et al 2005	Sertindole for schizophrenia.	Cochrane Database of Systematic Reviews. 2005, Issue 3.
Komossa K et al 2009	Sertindole versus other atypical antipsychotics for schizophrenia.	Cochrane Database of Systematic Reviews. 2009, issue 1.
Duggan L et al 2005	Olanzapine for schizophrenia.	Cochrane Database of Systematic Reviews. 2005, Issue 2.
Komossa K et al 2010	Olanzapine versus other atypical antipsychotics for schizophrenia.	Cochrane Database of Systematic Reviews. 2010, Issue 6.

8. Results of Trials

Sertindole vs risperidone

The submission presented results for the primary outcome in trials M95-372 and 97203, mean difference (sertindole – risperidone) in change from baseline in Positive And Negative Syndrome Scale (PANSS) total score at 12 weeks.

There was no statistically significant difference in the primary outcome of mean difference in change from baseline Positive and Negative Syndrome Scale (PANSS) total score at 12 weeks in the pooled results of trials M95-372 and 97203 for the post hoc analysis using last observation carried forward (LOCF). However, the post hoc analysis using LOCF did not meet the non-inferiority margin of a 7 point difference in PANSS total score, as previously accepted by the PBAC.

The submission also presented the mean difference (sertindole – risperidone) in change from baseline in PANSS and CGI-S scores at 12 weeks - post hoc analyses (LOCF) of trials M95-372 and 97203.

Statistically significant differences were not observed for the secondary outcomes of change from baseline PANSS subscale scores and Clinical Global Impression Severity (CGI-S) scale scores.

There were no statistically significant differences in proportions of responders (≥ 40% improvement in PANSS Total score) for trials M95-372 and 97203 between sertindole and

risperidone in either trial, although there were numerically more responders in the risperidone treated arms.

For PBAC's comments on these results, see Recommendation and Reasons.

Sertindole vs olanzapine (direct comparison)
A non-inferiority criterion of an upper confidence interval for treatment difference of ≤ 7.0 (PANSS total score) was pre-specified.

The submission presented the primary & secondary outcomes in Trial 11286, mean difference (sertindole – olanzapine) in change from baseline in PANSS and CGI-S scores at 12 weeks (LOCF).

Olanzapine treated patients showed numerically larger reductions in PANSS total score and the upper confidence interval for the mean difference in change from baseline PANSS total score did not meet the trial's pre-specified non-inferiority criterion.

There were statistically significantly more responders (by improvement in PANSS Total score; olanzapine/sertindole in the Full Analysis Set (FAS) population) in olanzapine treated patients than sertindole treated patients using both the LOCF and the observed cases (OC) approach to missing data, at both ≥ 25% and ≥ 35% decreases in PANSS Total scores and at all time points.

For PBAC's comments on these results, see Recommendation and Reasons.

Sertindole vs olanzapine (indirect comparisons)
The results for the indirect comparison (pooled olanzapine – pooled sertindole) with haloperidol as common comparator of mean difference in change from baseline in PANSS, Brief Psychiatric rating Scale (BPRS) and CGI-S indicated that there are statistically significant differences favouring olanzapine compared to sertindole in mean change from baseline PANSS (including Total score and all sub scales excluding Negative score) and BPRS scores at 12 weeks.

The submission compared the safety of sertindole with risperidone in the long term, open label post-marketing safety trial 99824 (designed to investigate whether treatment with sertindole increased all cause mortality, cardiac mortality and cardiac related hospitalisations compared to treatment with risperidone, requested as a condition of resumption of registration by the EMEA) and the direct randomised controlled trials M95-372 and 97203, and with olanzapine in the direct randomised controlled trial 11286.

The PBAC noted the results of the safety study 99824 showed statistically significantly higher rates of cardiac deaths (Independent Safety Committee (ISC)), and a higher rate of discontinuation of treatment in patients treated with sertindole compared to risperidone. There was no statistically significantly difference in cardiac events (including arrhythmias, requiring hospitalisation), fatal and non-fatal suicide attempts (ISC) and all cause mortality. All cause mortality was low in both cohorts.

The PBAC noted that there was a lower rate of suicides in sertindole treated patients compared to risperidone treated patients, however the difference was not statistically significant.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission described sertindole as non-inferior in terms of comparative effectiveness and equivalent in terms of comparative safety compared to risperidone or olanzapine, which the PBAC did not accept.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis versus risperidone. The equi-effective doses are estimated as sertindole 19 mg daily and risperidone 8 mg daily. For the alternative comparator the equi-effective doses are estimated as sertindole 16 mg daily and olanzapine 10 mg daily.

11. Estimated PBS Usage and Financial Implications

The financial savings/year to the PBS were estimated by the submission to be less than $500,000 in Year 5.

12. Recommendation and Reasons

The PBAC noted that the requested restriction for use in patients who have had prior treatment with at least one other anti-psychotic would allow use in a broader patient population than that specified the TGA approved indication, which limits use to patients who are not responsive to, or intolerant of at least one other anti-psychotic medicine.

The PBAC considered that olanzapine was a more appropriate choice of main comparator than risperidone, noting evidence from the survey of clinicians presented in the submission and supportive Medicare Australia data, which indicated that olanzapine was likely to be the most frequently prescribed atypical anti-psychotic in the second-line setting.

For the comparison of sertindole versus risperidone, the PBAC noted that there was no statistically significant difference in the primary outcome of mean difference in change from baseline Positive and Negative Syndrome Scale (PANSS) total score at 12 weeks in the pooled results of trials M95-372 and 97203 for the post hoc analysis using LOCF, however the post hoc analysis using LOCF did not meet the non-inferiority margin of a 7 point difference in PANSS total score, as previously accepted by the PBAC. Statistically significant differences were not observed for the secondary outcomes of change from baseline PANSS subscale scores and Clinical Global Impression Severity (CGI-S) scale scores.

For the comparison of sertindole versus olanzapine, the PBAC noted the results for the primary outcome of trial 11268 did not support the claim that sertindole is non-inferior to olanzapine. Olanzapine treated patients showed numerically larger reductions in PANSS total score and the upper confidence interval for the mean difference in change from baseline PANSS total score did not meet the trial's pre-specified non-inferiority criterion.

The PBAC noted the results of the safety study 99824 showed statistically significantly higher rates of cardiac deaths (Independent Safety Committee (ISC)), and a higher rate of discontinuation of treatment in patients treated with sertindole compared to risperidone. There was no statistically significantly difference in cardiac events (including arrhythmias, requiring hospitalisation), fatal and non-fatal suicide attempts (ISC) and all cause mortality. All cause mortality was low in both cohorts.

The PBAC noted that QT interval prolongation, in particular QTc (heart rate corrected QT) was reported more frequently in sertindole treated patients than risperidone treated patients in the direct randomised trials and appeared to be dose related. The PBAC noted that there is an association between prolonged QTc and the potentially fatal ventricular tachyarrthymia, Torsades de Pointes.

The PBAC accepted that treatment with sertindole was associated with a lower rate of extrapyramidal side effects than risperidone.

The PBAC was concerned that potentially serious drug interactions with sertindole were not addressed in the submission. The PBAC noted that sertindole is a substrate for the cytochrome P450 CYP2D6and CYP3A isozymes, which can be inhibited by a number of commonly prescribed drugs including fluoxetine and paroxetine, however, SSRIs may be given concurrently for co-morbid depression and obsessive-compulsive disorder in this patient population. The PBAC was also concerned that the question of cross-tapering with other anti-psychotic agents was not addressed in the submission, particularly given the slow onset of action of sertindole.

Overall, the PBAC did not accept the submission's claim that sertindole is non-inferior in terms of comparative efficacy and equivalent in terms of comparative safety compared to risperidone or olanzapine.

The PBAC noted the sponsor's Pre-PBAC Response and the clinician's opinion at the hearing, that there is a high clinical need for additional anti-psychotic treatment options in a few patients who derive no benefit from existing treatments, and those who are only partially responsive. However, the PBAC considered that the current average market share of sertindole in European markets did not support the existence of a high clinical need. The PBAC noted that no evidence of the efficacy of sertindole in treatment resistant patients had been presented in the submission, and that there are a number of PBS-subsidised treatment options currently available for this patient population. There are also options, other than olanzapine, for patients with metabolic syndrome or diabetes risks. Thus, the clinical need was not clearly established and did not justify the PBS listing of sertindole treatment given the safety risks.

The PBAC therefore rejected the submission, on the basis of uncertain clinical need, and concerns regarding relative efficacy, cardiovascular adverse effects and potential drug interactions.

The PBAC acknowledged and noted the consumer comments on this item.

Recommendation:

Reject

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor disagrees with the PBAC's comments on the comparator, and continues to believe that there is a high clinical need for Serdolect in a subpopulation of Australian schizophrenia patients. The sponsor would also like to point out that there is a risk management plan in place to minimise potential cardiac risk associated with Serdolect.